HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MENVEO safely and effectively. See full prescribing information for MENVEO.

MENVEO® [Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine]
Solution for intramuscular injection
Initial U.S. Approval: 2010

-INDICATIONS AND USAGE
MENVEO is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135. MENVEO is approved for use in persons 11 to 55 years of age. (1)

-DOSAGE AND ADMINISTRATION--
Administer MENVEO as a single 0.5 mL intramuscular injection after reconstitution. (2.1)

MENVEO consists of a liquid vaccine component (MenCYW-135 liquid conjugate component) and a lyophilized vaccine component (MenA lyophilized conjugate component). Reconstitute the MenA lyophilized conjugate component with the MenCYW-135 liquid conjugate component immediately before administration. (2.1)

-DOSAGE FORMS AND STRENGTHS-
Solution for injection (0.5-mL dose) supplied as a liquid vaccine component that is combined through reconstitution with a lyophilized vaccine component, both in single dose vials. (3)

CONTRAINDICATIONS
Severe allergic reaction (e.g., anaphylaxis) after a previous dose of MENVEO, any component of this vaccine, or any other CRM_{197}, diphtheria toxoid or meningococcal-containing vaccine is a contraindication to administration of MENVEO. (4)

WARNINGS AND PRECAUTIONS-
Appropriate medical treatment must be available should an acute allergic reaction, including an anaphylactic reaction, occur following administration of MENVEO. (5.1)

ADVERSE REACTIONS-
In clinical trials, the most frequently occurring adverse events in all subjects who received MENVEO were pain at the injection site (41%), headache (30%), myalgia (18%), malaise (16%) and nausea (10%). (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Vaccines at 1-877-683-4732 or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

-DRUG INTERACTIONS-
Do not mix MENVEO or any of its components with any other vaccine or diluent in the same syringe or vial. (7.1.)

----------USE IN SPECIFIC POPULATIONS----------
Safety and effectiveness of MENVEO have not been established in pregnant women. MENVEO should be given to a pregnant woman only if clearly needed. To enroll in the Novartis Vaccines and Diagnostics Inc. pregnancy registry, please call 1-877-311-8972. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: February 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

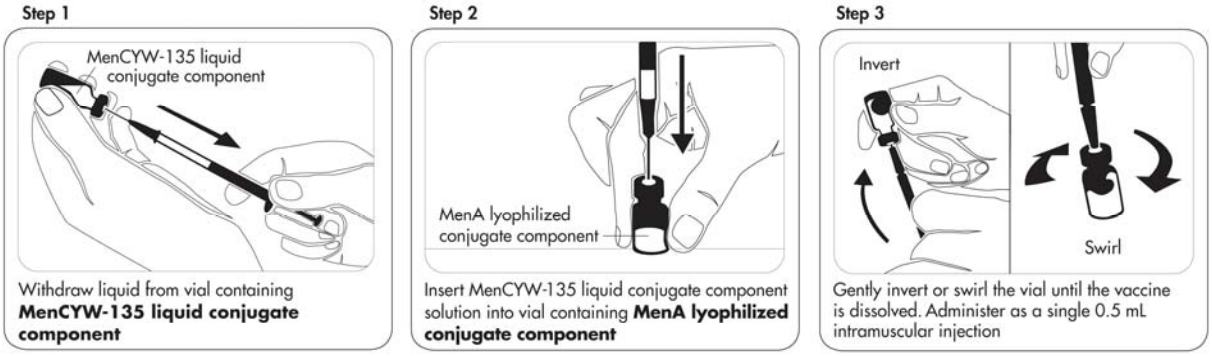
MENVEO is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135. MENVEO is approved for use in persons 11 to 55 years of age.

MENVEO does not prevent *N. meningitidis* serogroup B infections.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

MENVEO must be prepared for administration by reconstituting the MenA lyophilized conjugate component with the MenCYW-135 liquid conjugate component. Using a graduated syringe, withdraw the entire contents of the vial of MenCYW-135 liquid conjugate component and inject into the MenA lyophilized conjugate component vial. Gently invert or swirl the reconstituted vial until the vaccine is dissolved and then withdraw 0.5mL of reconstituted product.



Please note that it is normal for a small amount of liquid to remain in the vial following withdrawal of the dose.

Following reconstitution, the vaccine is a clear, colorless solution, free from visible foreign particles. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If any of these conditions exist, MENVEO should not be administered.

The reconstituted vaccine should be used immediately, but may be held at or below 77°F (25°C) for up to 8 hours.

2.2 Dose and Schedule

MENVEO should be administered as a single 0.5mL intramuscular injection, preferably into the deltoid muscle (upper arm). Do not administer MENVEO intravenously, subcutaneously or intradermally.

The duration of protection following immunization is not known.

3 DOSAGE FORMS AND STRENGTHS

MENVEO is a solution for intramuscular injection (0.5-mL dose) supplied as a liquid vaccine component that is combined through reconstitution with a lyophilized vaccine component, both in single dose vials. [See *Dosage and Administration (2.1), How Supplied/Storage and Handling (16)*].

4 CONTRAINDICATIONS

Severe allergic reaction (e.g. anaphylaxis) after a previous dose of MENVEO, any component of this vaccine, or any other CRM_{197}, diphtheria toxoid or meningococcal-containing vaccine is a contraindication to administration of MENVEO. [See *Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment must be available should an acute allergic reaction, including an anaphylactic reaction, occur following administration of MENVEO.

5.2 Syncope

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with MENVEO. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

5.3 Altered Immunocompetence

Safety and effectiveness of MENVEO have not been evaluated in immunocompromised persons. If MENVEO is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.4 Guillain-Barré Syndrome

Following vaccination with a U.S.-licensed meningococcal quadrivalent polysaccharide conjugate vaccine, an evaluation of post-marketing adverse events suggested a potential for an increased risk of Guillain-Barré Syndrome (GBS)(1). Data are not available to evaluate the potential risk of GBS following administration of MENVEO.

5.5 Bleeding Disorders

MENVEO should not be administered to persons with any bleeding disorder, or persons receiving anticoagulant therapy, unless the potential benefit outweighs the risk of administration.

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6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of MENVEO was evaluated in 5 randomized controlled clinical trials in which 6185 participants, 11 to 55 years of age received MENVEO (5286 received MENVEO alone and 899 received MENVEO concomitant with other vaccine(s) (Tetanus, Reduced Diphtheria and Acellular Pertussis Vaccine, Adsorbed (Boostrix®, GlaxoSmithKline Biologicals, Inc.), or with Boostrix plus Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18) Vaccine, Recombinant (GARDASIL®, Merck & Co., Inc.) and 1966 participants who received a comparator vaccine (either Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined - Menomune® , Sanofi Pasteur [N=209], or Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine - Menactra® , Sanofi Pasteur [N=1757])). The trials were conducted in North America, Latin America and Europe. In two of the studies, subjects received concomitant vaccination with Boostrix, or with Boostrix plus GARDASIL. Overall, subjects were white (50%), followed by Hispanic (40%), black (7%), and other racial/ethnic groups (3%). Among MENVEO recipients, 61%, 17% and 22% were in the 11 to 18 year, 19 to 34 year and 35 to 55 year age groups, respectively, with a mean age of 23.5 years (SD 12.9 years). Among Menactra recipients, 31%, 32% and 37% were in the 11 to 18 year, 19 to 34 year and 35 to 55 year age groups, respectively, with a mean age of 29.2 years (SD 13.4 years). Among Menomune recipients, 100% were in the 11 to 18 year age group, and the mean age was 14.2 years (SD 1.8 years).

Solicited local reactions and systemic adverse events were monitored daily for 7 days following vaccination and recorded on a diary card. Participants were monitored for 28 days for unsolicited adverse events which included adverse events requiring a physician visit, Emergency Department visit or which led to a subject's withdrawal from the study. Medically significant adverse events and serious adverse events (SAE) were monitored for 6 months after vaccination.

6.2 Solicited Adverse Reactions

In clinical trials, the most frequently occurring adverse events in all subjects who received MENVEO were pain at the injection site (41%), headache (30%), myalgia (18%), malaise (16%) and nausea (10%).

In a randomized controlled multicenter study conducted in the U.S., the most commonly reported solicited adverse events following administration of MENVEO to adolescents and adults were injection site pain and headache. The rates of these solicited adverse events were comparable to those reported following Menactra. The reported frequency and severity of local reactions and systemic adverse events that occurred within 7 days following the administration of MENVEO or Menactra to adolescents and adults are presented in Table 1 and Table 2. Neither study vaccine was administered with concomitant vaccines.

Table 1: Percentage of participants 11 to 18 years of age reporting solicited reactions during the 7 days following vaccination

	MENVEO N = 1631 %			Menactra N=539 %		
Reaction	**Any**	**Moderate**	**Severe**	**Any**	**Moderate**	**Severe**
Local						
Injection site pain[§]	44	9	1	53	11	1
Erythema[¥]	15	2	<1	16	1	0
Induration[¥]	12	2	<1	11	1	0
Systemic						
Headache[§]	29	8	2	28	7	1
Myalgia[§]	19	4	1	18	5	<1
Nausea[§]	12	3	1	9	2	1
Malaise[§]	11	3	1	12	5	1
Chills[§]	8	2	1	7	1	<1
Arthralgia[§]	8	2	<1	6	1	0
Rash*	3	-	-	3	-	-
Fever[†]	1	<1	0	1	0	0

[§] Moderate: Some limitation in normal daily activity, Severe: Unable to perform normal daily activity

[¥] Moderate: >50-100mm, Severe: > 100mm

* Rash was assessed only as present or not present, without a grading for severity.

[†] Moderate: 39-39.9°C, Severe: ≥ 40°C

Table 2: Percentage of participants 19 to 55 years of age reporting solicited reactions during the 7 days following vaccination

	MENVEO N=1018 %			Menactra N= 336 %		
Reaction	**Any**	**Moderate**	**Severe**	**Any**	**Moderate**	**Severe**
Local						
Injection site pain[§]	38	7	<1	41	6	0
Erythema[¥]	16	2	1	12	1	0
Induration[¥]	13	1	<1	9	<1	0
Systemic						
Headache[§]	25	7	2	25	7	1
Myalgia[§]	14	4	<1	15	3	1
Malaise[§]	10	3	1	10	2	1
Nausea[§]	7	2	<1	5	1	<1
Arthralgia[§]	6	2	<1	6	1	1
Chills[§]	4	1	<1	4	1	0
Rash*	2	-	-	1	-	-
Fever[†]	1	<1	0	1	<1	0

[§] Moderate: Some limitation in normal daily activity, Severe: Unable to perform normal daily activity.

[¥] Moderate: >50-100mm, Severe: > 100mm

* Rash was assessed only as present or not present, without a grading for severity.

[†] Moderate: 39-39.9°C, Severe: ≥ 40°C

The safety of MENVEO administered concomitantly with Boostrix and GARDASIL was evaluated in a single center study conducted in Costa Rica. Solicited local and systemic adverse events were recorded and reported as noted above. In this study, subjects 11 to 18 years of age received MENVEO concomitantly with Boostrix and GARDASIL (N=540), or MENVEO followed one month later by Boostrix and then one month later GARDASIL (N=541), or Boostrix followed one month later by MENVEO and then one month later GARDASIL (N=539). Some solicited systemic adverse events were more frequently reported in the group that received MENVEO, Boostrix and GARDASIL concomitantly, (headache 40%, malaise 25%, myalgia 27%, and arthralgia 17%) compared to the group that first received MENVEO alone (headache 36%, malaise 20%, myalgia 19%, and arthralgia 11%). Among subjects administered

MENVEO alone (one month prior to Boostrix), 36% reported headache, 20% malaise, and 16% myalgia. Among subjects administered MENVEO one month after Boostrix, 27% reported headache, 18% malaise, and 16% myalgia.

6.3 Serious Adverse Events in All Safety Studies

The information regarding serious adverse events was derived from 5 randomized, controlled clinical trials. Serious adverse events reported within 6 months of vaccination occurred in 40/6185 (0.6%) of MENVEO subjects, 13/1757 (0.7%) of Menactra subjects, and 5/209 (2.4%) of Menomune subjects. During the 6 months following immunization, SAEs reported by more than one subject were as follows: MENVEO - appendicitis (3 subjects), road traffic accident (3 subjects), and suicide attempt (5 subjects); Menactra - intervertebral disc protrusion (2 subjects); Menomune - none. Serious adverse events that occurred within 30 days of vaccination were reported by 7 of 6185 (0.1%) subjects in the MENVEO group, 4 of 1757 (0.2%) subjects in the Menactra group, and no Menomune subjects. The events that occurred during the first 30 days post immunization with MENVEO were: vitello-intestinal duct remnant; Cushing's syndrome; viral hepatitis; pelvic inflammatory disease; intentional multiple drug overdose; simple partial seizure; and suicidal depression. The events that occurred during the first 30 days post immunization with Menactra were: herpes zoster; fall; intervertebral disc protrusion; and angioedema.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

Do not mix MENVEO or any of its components with any other vaccine or diluent in the same syringe or vial.

In a clinical trial in which MENVEO was given concomitantly with Boostrix and GARDASIL, no interference was observed in meningococcal immune responses when compared to MENVEO given alone. Lower geometric mean antibody concentrations (GMCs) for antibodies to the pertussis antigens filamentous hemagglutinin (FHA) and pertactin were observed when MENVEO was administered concomitantly with Boostrix and GARDASIL as compared with Boostrix alone. [*Immunogenicity of Concomitantly Administered Vaccines, 14.3*]

7.2 Immunosuppressive Treatments

Immunosuppressive therapies, such as irradiation, antimetabolite medications, alkylating agents, cytotoxic drugs, and corticosteroids (when used in greater than physiologic doses) may reduce the immune response to MENVEO [*See Warnings and Precautions (5.3)*]. The immunogenicity of MENVEO has not been evaluated in persons receiving such therapies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in female rabbits at a dose of approximately 20 times the human dose (on a mg/kg basis) and have revealed no evidence of impaired fertility or harm to the fetus due to MENVEO. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, MENVEO should be given to a pregnant woman only if clearly needed.

Nonclinical Studies

The effect of MENVEO on embryo-fetal and post-natal development was evaluated in pregnant rabbits. Animals were administered MENVEO 3 times prior to gestation, during the period of organogenesis (gestation day 7) and later in pregnancy (gestation day 20), 0.5 ml/rabbit/occasion (approximately 20-fold excess relative to the projected human dose on a body weight basis) by intramuscular injections. There were no adverse effects attributable to the vaccine on mating, female fertility, pregnancy, or embryo-fetal development. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study.

Clinical Studies

To date, no clinical trials have been specifically designed to evaluate the use of MENVEO in pregnant or lactating women. Among the 5209 women enrolled in the studies, 43 women were found to be pregnant during the 6-month follow-up period after vaccination. Of these, 37 pregnancies occurred among 4115 MENVEO recipients (7 spontaneous abortions, no congenital anomalies). Six pregnancies occurred among 1013 Menactra recipients (no spontaneous abortions, one congenital anomaly (hydrocephalus)). Among the seven subjects with adverse pregnancy outcomes who had received MENVEO, the estimated dates of conception were 5 days prior to

vaccination (1 subject), 6 to 17 weeks post vaccination (5 subjects), and 6 months post vaccination (1 subject). In the subject who had received Menactra the estimated date of conception was approximately 15 weeks post immunization.

Safety and effectiveness of MENVEO have not been established in pregnant women. To enroll in the Novartis Vaccines and Diagnostics Inc. pregnancy registry, please call 1-877-311-8972.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MENVEO is administered to a nursing woman. No studies have been conducted to assess the impact of MENVEO on milk production, its presence in breast milk or its effects on the breast-fed child.

8.4 Pediatric Populations

Safety and effectiveness of MENVEO in children under 11 years old have not been established.

8.5 Geriatric Populations

Safety and effectiveness of MENVEO in adults 65 years of age and older have not been established .

11 DESCRIPTION

MENVEO [Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine] is a sterile liquid vaccine administered by intramuscular injection that contains *N. meningitidis* serogroup A, C, Y and W-135 oligosaccharides conjugated individually to *Corynebacterium diphtheriae* CRM_{197} protein. The polysaccharides are produced by bacterial fermentation of *N. meningitidis* (serogroups A, C, Y or W-135). *N. meningitidis* strains A, C, Y and W-135 are each cultured and grown on Franz Complete medium and treated with formaldehyde. MenA, MenW-135 and MenY polysaccharides are purified by several extraction and precipitation steps. MenC polysaccharide is purified by a combination of chromatography and precipitation steps.

The protein carrier (CRM_{197}) is produced by bacterial fermentation and is purified by a series of chromatography and ultrafiltration steps. *C. diphtheriae* is cultured and grown on CY medium containing yeast extracts and amino acids.

The oligosaccharides are prepared for conjugation from purified polysaccharides by hydrolysis, sizing, and reductive amination. After activation, each oligosaccharide is covalently linked to the CRM_{197} protein. The resulting glycoconjugates are purified to yield the four drug substances, which compose the final vaccine. The vaccine contains no preservative or adjuvant. Each dose of vaccine contains 10 µg MenA oligosaccharide, 5 µg of each of MenC, MenY and MenW-135 oligosaccharides and 32.7 to 64.1 µg CRM_{197} protein. Residual formaldehyde per dose is estimated to be not more than 0.30 µg.

The vials in which the vaccine components are contained are composed of Type I glass, USP. The container closures (synthetic rubber stoppers) do not contain latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Neisseria meningitidis is a gram-negative diplococcus that causes life-threatening invasive disease such as meningitis and sepsis. Globally, 5 serogroups, A, B, C, Y and W-135 cause almost all invasive meningococcal infections. The presence of serum bactericidal antibodies protects against invasive meningococcal disease (2). Vaccination with MENVEO leads to the production of bactericidal antibodies directed against the capsular polysaccharides of serogroups A, C, Y and W-135.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

MENVEO has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility.

14 CLINICAL STUDIES

The effectiveness of MENVEO among subjects aged 11 to 55 years has been inferred from the demonstration of non-inferiority of the serum bactericidal antibody responses to those of Menactra. Serogroup-specific anticapsular antibodies with bactericidal activity were measured using pooled human serum that lacked bactericidal activity as the source of exogenous complement (hSBA).

Immunogenicity was evaluated in a randomized, multicenter, active controlled clinical trial conducted in the U.S. that enrolled adolescents (11 to 18 years of age) and adults (19 to 55 years of age). The trial enrolled 3539 participants, who were randomized to receive a dose of MENVEO (N=2663) or Menactra (N=876). Sera were obtained both before vaccination and 28 days after vaccination. The primary effectiveness endpoints of the study were hSBA seroresponse rates to each serogroup 28 days after vaccination. Seroresponse was defined as: for subjects with a pre-vaccination hSBA titer of <1:4, a post vaccination titer of $\geq$ 1:8 and among subjects with a pre-vaccination hSBA titer of $\geq$ 1:4, a post vaccination titer at least 4-fold higher than baseline. Secondary endpoints were the proportion of subjects with hSBA antibody titer $\geq$1:8 and the hSBA GMTs to each serogroup. Among subjects who completed the per-protocol evaluation for immunogenicity (N=3393, MENVEO= 2549, Menactra=844), demographic characteristics for MENVEO and Menactra subjects respectively were similar: mean age 23.9 (SD 13.6) vs. 23.7 (SD 13.7), 42% vs. 42% male, 79% vs. 78% Caucasian, 8% vs. 9% African American, 7% vs. 7% Hispanic, 3% vs. 3% Asian, 2% vs. 3% Other. Immunogenicity for each serogroup was assessed in a subset of study participants (see Tables 3 and 4).

14.1 Immunogenicity in Adolescents

In study participants aged 11-18 years, non-inferiority of MENVEO to Menactra was demonstrated for all four serogroups using the primary endpoint (hSBA seroresponse) (Table 3). The percentages of subjects with hSBA seroresponse were statistically higher for serogroups A, W, and Y in the MENVEO group, as compared to the Menactra group, however the clinical relevance of higher post-vaccination immune responses is not known.

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Table 3: Comparison of bactericidal antibody responses† to MENVEO and Menactra 28 days after vaccination of subjects aged 11-18 years

	Bactericidal Antibody Response†		Comparison of MENVEO and Menactra	
Endpoint by Serogroup	**MENVEO (95% CI)**	**Menactra (95% CI)**	**MENVEO / Menactra (95% CI)**	**MENVEO minus Menactra (95% CI)**
A	N=1075	N=359		
% Seroresponse‡	75 (72, 77)	66 (61, 71)		8 (3, 14)* §
% ≥ 1:8	75 (73 , 78)	67 (62, 72)	-	8 (3, 14)
GMT	29 (24 , 35)	18 (14, 23)	1.63 (1.31, 2.02)	-
C	N=1483	N=501		
% Seroresponse‡	75 (73, 77)	73 (69, 77)		2 (-2, 7)*
% ≥ 1:8	84 (82, 86)	84 (80, 87)	-	1 (-3, 5)
GMT	59 (48, 73)	47 (36, 61)	1.27 (1.01, 1.6)	-
W-135	N=1024	N=288		
% Seroresponse‡	75 (72, 77)	63 (57, 68)		12 (6, 18)*§
% ≥ 1:8	96 (95, 97)	88 (84, 92)	-	8 (4, 12)
GMT	87 (74, 102)	44 (35, 54)	2.00 (1.66, 2.42)	-
Y	N=1036	N=294		
% Seroresponse‡	68 (65, 71)	41 (35, 47)		27 (20, 33)* §
% ≥ 1:8	88 (85, 90)	69 (63, 74)	-	19 (14, 25)
GMT	51 (42, 61)	18 (14, 23)	2.82 (2.26, 3.52)	-

† Serum Bactericidal Assay with exogenous human complement source (hSBA).

‡ Seroresponse was defined as: subjects with a pre-vaccination hSBA titer of <1:4, a post vaccination titer of ≥ 1:8 and among subjects with a pre-vaccination hSBA titer of ≥ 1:4, a post vaccination titer at least 4-fold higher than baseline.

* Non-inferiority criterion for the primary endpoint met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences [MENVEO minus Menactra]). The clinical relevance of higher post-vaccination immune responses is not known.

§ The seroresponse was statistically higher (the lower limit of the two-sided 95% CI >0% for vaccine group differences); however the clinical relevance of higher post-vaccination immune responses is not known.

14.2 Immunogenicity in Adults

In study participants aged 19-55 years, non-inferiority of MENVEO to Menactra was demonstrated for all four serogroups using the primary endpoint (hSBA seroresponse) (Table 4). The percentage of subjects with hSBA seroresponse was statistically higher for serogroups C, W, and Y in the MENVEO group, as compared to the Menactra group; however the clinical relevance of higher post-vaccination immune responses is not known.

Table 4: Comparison of bactericidal antibody responses† to MENVEO and Menactra 28 days after vaccination of subjects aged 19 to 55 years

	Bactericidal Antibody Response†		Comparison of MENVEO and Menactra	
Endpoint by Serogroup	**MENVEO (95% CI)**	**Menactra (95% CI)**	**MENVEO / Menactra (95% CI)**	**MENVEO minus Menactra (95% CI)**
A	N=963	N=321		
% Seroresponse‡	67 (64, 70)	68 (63, 73)		-1 (-7, 5)*
% ≥ 1:8	69 (66, 72)	71 (65, 76)	-	-2 (-7, 4)
GMT	31 (27, 36)	30 (24, 37)	1.06 (0.82, 1.37)	-
C	N=961	N=318		
% Seroresponse‡	67 (64, 70)	58 (53, 64)		9 (3, 15)* §
% ≥ 1:8	80 (77, 83)	72 (67, 77)	-	8 (3, 14)
GMT	52 (44, 60)	32 (25, 40)	1.63 (1.24, 2.13)	-
W-135	N=484	N=292		
% Seroresponse‡	50 (46, 55)	41 (35, 47)		9 (2, 17)* §
% ≥ 1:8	94 (91, 96)	90 (86, 93)	-	4 (0, 9)
GMT	111 (93, 132)	69 (55, 85)	1.61 (1.24, 2.1)	-
Y	N=503	N=306		
% Seroresponse‡	56 (51, 60)	40 (34, 46)		16 (9, 23)* §
% ≥ 1:8	79 (76, 83)	70 (65, 75)	-	9 (3, 15)
GMT	44 (37, 52)	21 (17, 26)	2.10 (1.60, 2.75)	-

† Serum Bactericidal Assay with exogenous human complement source (hSBA).

‡ Seroresponse was defined as: subjects with a pre-vaccination hSBA titer of <1:4, a post vaccination titer of ≥ 1:8 and among subjects with a pre-vaccination hSBA titer of ≥ 1:4, a post vaccination titer at least 4-fold higher than baseline.

* Non-inferiority criterion for the primary endpoint met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences [MENVEO minus Menactra]). The clinical relevance of higher post-vaccination immune responses is not known.

§ The seroresponse was statistically higher (the lower limit of the two-sided 95% CI >0% for vaccine group differences); however the clinical relevance of higher post-vaccination immune responses is not known.

14.3 Immunogenicity of Concomitantly Administered Vaccines

A trial was conducted in Costa Rica to assess the effect of concomitant administration of MENVEO with Boostrix and GARDASIL (see also section 7.1 for the safety results from this trial). Subjects were randomized to receive one of the following regimens at the start of the trial: MENVEO plus Boostrix plus GARDASIL (N=540); MENVEO alone (N=541); Boostrix alone (N=539). Subjects were healthy adolescents aged 11 to 18 years (mean age between groups was 13.8 to 13.9 years). For MENVEO antigens, the proportion of subjects achieving an hSBA seroresponse among those who received MENVEO plus Boostrix plus GARDASIL vs. MENVEO alone, respectively, were: serogroup A 80% (76, 84) vs. 82% (78, 85); serogroup C 83% (79, 86) vs. 84% (81, 88); serogroup W 77% (73, 80) vs. 81% (77, 84); serogroup Y 83% (79, 86) vs. 82% (79, 86). Among subjects who received Boostrix plus

MENVEO plus GARDASIL, compared with Boostrix alone, the proportions of subjects who achieved a titer ≥1.0 IU/mL of Tetanus or Diphtheria antibodies in the two groups respectively was 100% (99, 100) , vs. 98% (96, 99). For pertussis antigens, among subjects who received Boostrix plus MENVEO plus GARDASIL, compared with Boostrix alone, the responses respectively for anti-pertussis toxin GMCs were 51 (47, 55) vs. 63 (58, 69) Elisa Units (EU)/mL, for anti-filamentous hemagglutinin were 342 (310, 376) vs. 511 (464, 563) EU/mL, and for anti-pertactin were 819 (727, 923) vs. 1197 (1061, 1350) EU/mL. Because there are no established serological correlates of protection for pertussis, the clinical implications of the lower pertussis antigen responses are unknown.

15 REFERENCES

1. Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report (MMWR) (2006) 55 (41): 1120-1124.
2. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med (1969);129:1307-1326.

16 HOW SUPPLIED, STORAGE AND HANDLING

16.1 How Supplied

MENVEO is supplied as a vial containing MenA lyophilized conjugate component and a vial containing MenCYW-135 liquid conjugate component (1 dose after reconstitution). There are five doses (10 vials) per package. The container closures (synthetic rubber stoppers) do not contain latex.

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16.2 Storage and Handling

Do not freeze. Frozen/previously frozen product should not be used.

Store refrigerated, away from the freezer compartment, at 36°F to 46°F (2°C to 8°C).

Protect from light. Vaccine must be maintained at 36°F to 46°F during transport.

Do not use after the expiration date. The reconstituted vaccine should be used immediately, but may be held at or below 77°F (25°C) for up to 8 hours.

17 PATIENT COUNSELING INFORMATION

Vaccine Information Statements are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization to the patient, parent, or guardian. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines.)

Patients, parents or guardians should be:

- Informed of the potential benefits and risks of immunization with MENVEO.
- Informed about the potential for adverse reactions that have been temporally associated with administration of MENVEO or other vaccines containing similar components.
- Instructed to report any adverse reactions to their healthcare provider.
- Informed about the Novartis Vaccines and Diagnostics Inc. pregnancy registry, as appropriate.

Manufactured by:
Novartis Vaccines and Diagnostics S.r.l.,
Bellaria-Rosia 53018, Sovicille (SI), Italy.

An affiliate of:
Novartis Vaccines and Diagnostics, Inc.
350 Massachusetts Avenue,
Cambridge, MA 02139-4182, USA
1-877-683-4732

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